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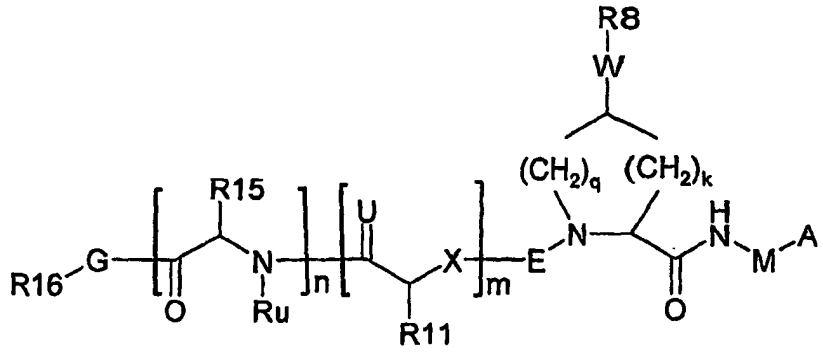
(54) Title: HCV NS-3 SERINE PROTEASE INHIBITORS



(57) Abstract: Compounds of the formula (F) where the variables are as defined in the specification inhibit the NS3 protease of flavivirus sych as hepatitis C virus (HCV). The compounds comprise a novel linkage between a heterocyclic P2 unit and those portions of the inhibitor more distal to the nominal cleavage site of the native substrate, which linkage reverses the orientation of peptidic bonds on the distal side relative to those proximal to the cleavage site.

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INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/SE2005/000096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/02 C07D401/12 C07D409/14 C07D405/14 C07D413/14
C07D417/14 C07D207/16 A61K31/47 A61P31/12 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/09543 A (BOEHRINGER INGELHEIM LTD; LLINAS-BRUNET, MONTSE; BAILEY, MURRAY, D; C) 24 February 2000 (2000-02-24) cited in the application claims	1-56
A	US 2003/186895 A1 (LLINAS-BRUNET MONTSE ET AL) 2 October 2003 (2003-10-02) claims	1-56
X	EP 0 443 132 A (FUJISAWA PHARMACEUTICAL CO., LTD) 28 August 1991 (1991-08-28) page 7, formula XI	1-5
X	EP 0 126 587 A (SUMITOMO CHEMICAL COMPANY, LIMITED; SUMITOMO PHARMACEUTICALS COMPANY,) 28 November 1984 (1984-11-28) page 53, reference example 1-25	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2005	12/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

INTERNATIONAL SEARCH REPORT

Inten ıl Application No
PC1/SE2005/000096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZANOTTI, GIANCARLO ET AL: "Synthesis of analogs of amaninamide, an amatoxin from the white Amanita virosa mushroom" INTERNATIONAL JOURNAL OF PEPTIDE & PROTEIN RESEARCH , 30(4), 450-9 CODEN: IJPPC3; ISSN: 0367-8377, 1987, XP008050698 compound with RN=112772-43-7; 112772-44-8; 112772-45-9 page 454, right-hand column, line 19 - line 32	1-5
X	ZANOTTI, GIANCARLO ET AL: "Analogs of amanin. Synthesis of Ile3-amaninamide and its diastereoisomeric (S)-sulfoxide" INTERNATIONAL JOURNAL OF PEPTIDE & PROTEIN RESEARCH , 18(2), 162-8 CODEN: IJPPC3; ISSN: 0367-8377, 1981, XP008050700 page 166, right-hand column, line 26	1-5
E	WO 2005/010029 A (ENANTA PHARMACEUTICALS, INC; WU, FRANK, X., H; NAKAJIMA, SUANNE; OR, Y) 3 February 2005 (2005-02-03) the whole document	1-56

INTERNATIONAL SEARCH REPORT

tional application No.
PCT/SE2005/000096

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 54,56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In Application No
PCT/SE2005/000096

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Int. Application No
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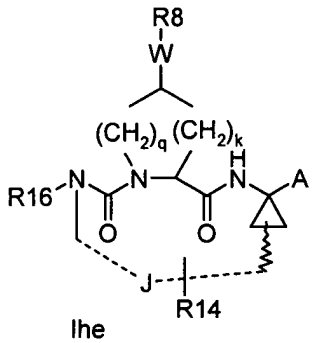
		WO 2005010029 A1	03-02-2005

New claims

57. A compound according to claim 1 with the formula Ihe



Ihe

wherein

R^{16} is H, or C_1-C_6alkyl;

J is a single 3 to 10-membered saturated or partially unsaturated alkylene chain;

q is 1 and k is 1;

A is C(=O)OR^1, or C(=O)$NHSO_2R^2$, wherein

R^1 is hydrogen or C_1-C_6alkyl;

R^2 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

W is -O- or -OC(=O)NH-;

R^8 is C_0-C_3alkylaryl or C_0-C_3alkylheteroaryl, either of which is optionally mono, di, or tri substituted with R^9, wherein;

R^9 is C_1-C_6alkyl, C_1-C_6alkoxy, NO_2, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C_1-C_6alkyl, C_0-C_3alkylaryl, C_0-C_3alkylheteroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R^{10}; wherein

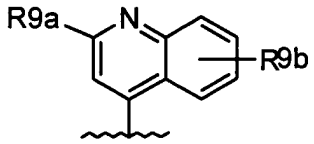
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, C_1-C_3 alkyl amide, sulfonylC_1-C_3alkyl, NO_2, OH, halo, trifluoromethyl, carboxyl or heteroaryl.

58. A compound according to claim 57, wherein J is a single 5- or 6-membered saturated or partially unsaturated alkylene chain.

59. A compound according to claims 57 or 58, wherein J is monounsaturated.

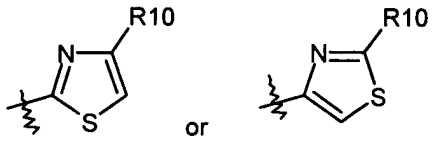
60. A compound according to claim 59, wherein J has one double bond spaced one carbon atom from the cyclopropyl group depicted in formula Ihe.

61. A compound according to claim 57-60, wherein R^8 is the group



wherein R^{9a} is C_0-C_3alkylaryl, C_0-C_3alkylheteroaryl, or C_0-C_3alkylheterocyclyl; said aryl, heteroaryl or heterocyclyl being optionally substituted with R^{10}
wherein R^{10} is C_1-C_6alkyl, amino, amino mono- or disubstituted with C_1-C_6alkyl or NHC(=O)C1-C6alkyl; and
R^{9b} is C_1-C_6-alkoxy; or
R^8 is C_0-C_3alkylaryl wherein the aryl group is optionally substituted with 1-2 substituents selected from C_0-C_3alkylheterocyclyl and trifluoC_1-C_6alkyl; and wherein the C_0-C_3alkylheterocyclyl is optionally substituted with R^{10}.

62. A compound according to claim 61, wherein R^{9a} is



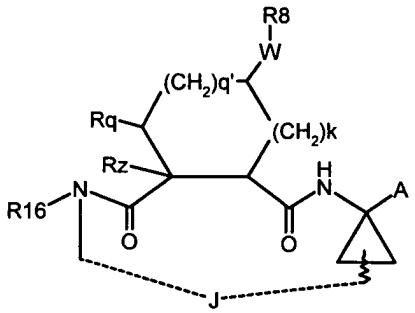
wherein R^{10} is H, C_1-C_6alkyl, amino, amino mono or disubstituted with C_1-C_3alkyl.

63. A compound according to any of claims 57-62, wherein A is $C(=O)NHS(=O)_2R^2$.

64. A compound according to claim 63, wherein R^2 is optionally substituted cycloalkyl, preferably cyclopropyl.

New claims

58. A compound according to claim 1 with the formula VIhe:



VIhe

wherein

R^{16} is H, C_1-C_6alkyl or C_0-C_3alkylcarbocyclyl;

J is a single 3 to 10-membered saturated or partially unsaturated alkylene chain;

Rz is H;

Rq is H;

q' is 0 and k is 1;

A is $C(=O)OR^1$ or $C(=O)NHSO_2R^2$, wherein

R^1 is hydrogen, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^2 is C_1-C_6alkyl or C_0-C_3alkylcarbocyclyl;

W is -O- or -OC(=O)NH-;

R^8 is C_0-C_3alkylaryl, or C_0-C_3alkylheteroaryl, either of which is optionally mono, di, or tri substituted with R^9, wherein;

R^9 is C_1-C_6alkyl, C_1-C_6alkoxy, NO_2, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C_1-C_6alkyl, C_0-C_3alkylaryl, C_0-C_3alkylheteroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R^{10}; wherein

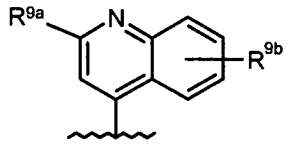
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, C_1-C_3 alkyl amide, sulfonylC_1-C_3alkyl, NO_2, OH, halo, trifluoromethyl, carboxyl, or heteroaryl.

59. A compound according to claim 58, wherein J is a 5- or 6-membered saturated or partially unsaturated alkylene chain.

60. A compound according to claims 58 or 59, wherein J is monounsaturated.

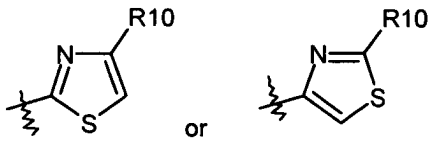
61. A compound according to claim 60, wherein J has one double bond spaced one carbon atom from the cyclopropyl group depicted in formula VIhe.

62. A compound according to any of claims 58-61 wherein R^8 is the group



wherein R^{9a} is C_0-C_3alkylaryl, C_0-C_3alkylheteroaryl or C_0-C_3alkylheterocyclyl; said aryl, heteroaryl or heterocyclyl being optionally substituted with R^{10}; wherein R^{10} is C_1-C_6alkyl, amino mono- or di-substituted with C_1-C_6alkyl; R^{9b} is C_1-C_6alkoxy; or
R^8 is C_0-C_3alkylaryl wherein the aryl group is optionally substituted with 1-2 substituents selected from C_0-C_3alkylheterocyclyl and trifluoC_1-C_6alkyl; and wherein the C_0-C_3alkylheterocyclyl is optionally substituted with R^{10}.

63. A compound according to claim 62, wherein R^{9a} is

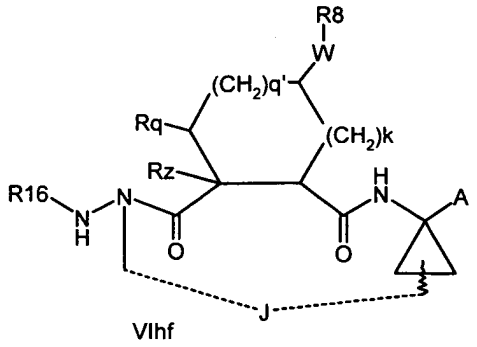


wherein R^{10} is H, C_1-C_6alkyl, amino, amino mono or disubstituted with C_1-C_3alkyl.

64. A compound according to any of claims 58-63, wherein A is $C(=O)NHS(=O)_2R^2$.

65. A compound according to claim 64, wherein R^2 is optionally substituted cycloalkyl, preferably cyclopropyl.

66. A compound according to claim 1 with the formula VIhf:



VIhf

wherein

R^{16} is H, C_1-C_6alkyl;

J is a single 3 to 10-membered saturated or partially unsaturated alkylene chain;

Rz is H;

Rq is H;

q' is 0 and k is 1;

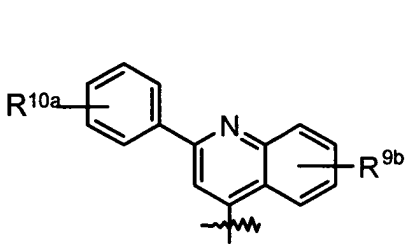
A is $C(=O)OR^1$ or $C(=O)NHSO_2R^2$, wherein

R^1 is hydrogen or C_1-C_6alkyl;

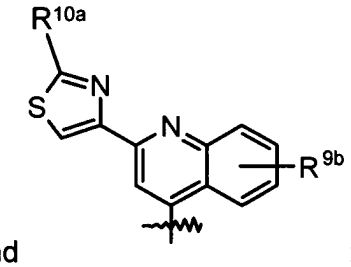
R^2 is C_1-C_6alkyl or C_0-C_3alkylcarbocyclyl;

W is -O-;

R^8 is a group selected from



and

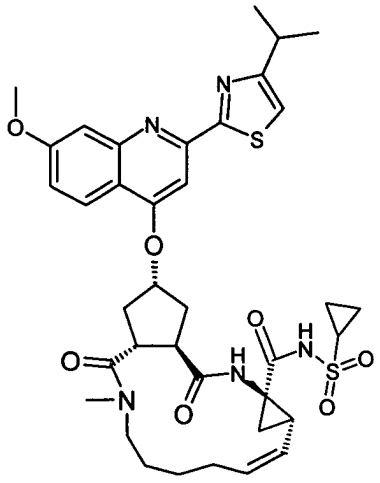


;

wherein

R^{10} is H, C_1-C_6alkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl and R^{9b} is C_1-C_6alkoxy.

67. A compound according to claim 58 with the formula



68. A compound according to claim 58 with the formula